

## **REMARKS**

### **Claim Amendments**

Claims 1-35 were previously withdrawn without prejudice as drawn to a non-elected invention. Applicant has amended claim 36 so that it is drawn to a method of cleaving RNA comprising SEQ ID NO:2456 encoded by a mammalian VEGFr1 gene (emphasis added). In addition, the nucleotide length limitation of claim 36 has been amended from 19-29 nucleotides to about 18 to about 27 nucleotides (emphasis added). Furthermore, the chemical modification limitation of claim 36 has been amended to be selected from the group consisting of 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoro nucleotide, and 2'-deoxy ribose moiety. Applicant has also amended claims 37, 38, 40 and 56 to remove the term "said". A complete listing of all the claims, in compliance with the revised amendment format, is shown above.

Amended claim 36 is fully supported by the specification as filed, for example, inter alia, at pages 7, 8, 9, 12, 33, 53, 69, and Tables I and II. Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

### **Claim Objections**

The Office objected to claims 36, 37, 38, 40 and 56 because of various informalities. Claim 36 has been amended to include the term "the" between the words "by" and "VEGFr1", and claims 37, 38, 40 and 56 have been amended to remove the term "said" as suggested.

### **35 USC § 112, First Paragraph Rejection**

The Office rejected claim 36 under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office alleges that the specification discloses one species of target VEGFr1 and one skilled in the art could not make oligos to any mammalian VEGFr1 gene without knowledge of the sequence. Thus, one could not envision member oligonucleotides that target any mammalian VEGFr1 gene as a genus.

While Applicant respectfully disagrees with the Office's argument, solely in the interest of expediting prosecution, Claim 36 has been amended to recite a method of cleaving RNA comprising SEQ ID NO: 2456 encoded by a mammalian VEGFr1 gene. The Office states that "the specification discloses double stranded nucleic acid sequences having complementarity to [this] VEGFr1 sequence". As indicated by the Office, Applicant submits that the claimed subject matter is described in such a way as to convey to one skilled in the art that Applicant had possession of the invention. Accordingly, Applicant respectfully requests withdrawal of the 35 USC §112, first paragraph rejection.

### **Priority**

The Office Action alleges that the instant application is not entitled to priority to any of the earlier filed priority documents because none of the documents teach methods of targeting VEGFr1 with 19-29 nucleotide dsRNA molecules. The Applicant respectfully disagrees. However, in the interest of advancing prosecution, claim 36 has been amended to recite a method of targeting VEGFr1 with a double-stranded nucleic acid molecule wherein each strand of the double-stranded nucleic acid molecule comprises about 18 to about 27 nucleotides.

The present application is a continuation-in-part of McSwiggen USSN 10/664,767, filed on September 16, 2003, USSN to be assigned, which is a continuation-in-part of McSwiggen, PCT/US03/05022, filed February 20, 2003, which claims the

benefit of Beigelman USSN 60/358,580 filed February 20, 2002, of Beigelman USSN 60/363,124 filed March 11, 2002, of Beigelman USSN 60/386,782 filed June 6, 2002, of McSwiggen, USSN 60/393,796 filed July 3, 2002, of McSwiggen, USSN 60/399,348 filed July 29, 2002, of Beigelman USSN 60/406,784 filed August 29, 2002, of Beigelman USSN 60/408,378 filed September 5, 2002, of Beigelman USSN 60/409,293 filed September 9, 2002, and of Beigelman USSN 60/440,129 filed January 15, 2003, and which is a continuation-in-part of Pavco, USSN 10/306,747, filed November 27, 2002, which claims the benefit of Pavco USSN 60/334461, filed November 30, 2001, a continuation-in-part of Pavco, USSN 10/287,949 filed November 4, 2002, and a continuation-in-part of Pavco, PCT/US02/17674 filed May 29, 2002.

The claims presented above all find support in, inter alia, the priority applications. For example, support for the “about 18 to about 27” nucleotide limitation of claim 36 can be found on page 12 of the 60/363,124 application and on page 9 of the 60/334,461 application. In addition, support for double stranded nucleic acid molecules targeting SEQ ID NO:2456 (corresponding to GenBank Accession No. NM\_002019 for VEGFr1 RNA) can be found in Table III of the 60/363,124 application and on page 55 of the 60/334,461 application. Therefore, the present invention is afforded a priority date of at least November 30, 2001.

### **35 USC § 102 Rejections**

Claims 36 and 38-52 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Lockridge et al., (US 2003/0216335). Applicants respectfully traverse the rejection.

Lockridge was filed on November 27, 2002, claiming priority to USSN 60/334,461 which was filed on November 30, 2001. It should be noted that Lockridge claims priority to the same provisional patent application as the instant application (USSN 60/334,461). For the reasons stated above, the instant application should be accorded an effective filing date of at least November 30, 2001. Thus, Lockridge is not

prior art to the instant application. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §102(e) rejection.

Claims 36, 38-40, 44, 47, 48, 50, and 52 stand rejected under 35 U.S.C. §102(a) or §102(e) as allegedly anticipated by Escobedo et al., (WO 02/096929). Applicants respectfully traverse the rejection.

As discussed above, the effective filing date of the instant invention is November 30, 2001 (see discussion of priority above). Escobedo et al. claims priority to (1) 10/138,674 filed May 3, 2002; (2) 60/334, 461 filed November 30, 2001; and (3) 09/870,161, filed May 29, 2001. Thus, the only priority application that is prior to the instant application is 09/870,161, filed May 29, 2001. Applicant submits that the 09/870,161 application does not describe the claimed subject matter of the instant application and therefore does not anticipate. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §102(a) or §102(e) rejection.

### **35 USC § 103 Rejection**

Claims 36-55 stand rejected as allegedly obvious over Tolentino et al. (US 2004/0018176), in view of Pavco et al. (US 6,346,398), Elbashir et al. (EMBO J., 20:6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, 1077-1087, 2000), Matulic Adamic et al. (US 5,998,203) and Cook et al. (US 5,587,471). The Applicants respectfully traverse.

Tolentino was filed on November 14, 2002 with priority stated to USSN 60/398,417, which was filed on July 24, 2002. Tolentino is therefore not prior art for the purpose of 35 USC §103(a) because the effective filing date of the instant application November 30, 2001 (see priority discussion above) precedes Tolentino.

The Office Action states that “[e]ven without Tolentino et al. art, the invention is still considered obvious in view of the antisense art that teaches targeting the same gene for sequence specific inhibition of gene expression” (Office Action at pages 10-11). The Applicants respectfully traverse, because, as explained below, the art cited in the Office Action actually taught away from the presently claimed invention. However, in the

interest of advancing prosecution, claim 36 has been amended to recite a method of cleaving RNA comprising SEQ ID NO:2456 encoded by a mammalian VEGFr1 gene comprising contacting a double-stranded nucleic acid molecule with the RNA encoded by VEGFr1 gene under conditions suitable for the cleavage of the RNA encoded by the mammalian VEGFr1 gene, wherein: (a) each strand of the double-stranded nucleic acid molecule comprises about 18 to about 27 nucleotides; (b) each strand of the double stranded nucleic acid molecule comprises *one or more chemical modifications selected from the group consisting of 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoro nucleotide, and 2'-deoxy ribose moiety*; and (c) one of the strands of the double stranded nucleic acid molecule is complementary to RNA encoded by the mammalian VEGFr1 gene or a portion thereof and the other strand is complementary to the first strand (*emphasis added*).

Applicants submit that the Office Action has not established a *prima facie* case of obviousness with regard to the instantly claimed invention. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. See MPEP §2143. -

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." See, *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., *Interconnect Planning Corp. v.*

*Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). “Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.” *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (“particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed”).

In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants’ disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

Elbashir teaches siRNA technology generally, but fails to teach, mention, or suggest double stranded nucleic acid molecules as presently claimed by virtue of the chemical modifications and the VEGFr1 target sequence recited by the instant claims. Parrish reports that duplexes only as short as 26 bp can trigger RNA, however, Parrish deals with a non-mammalian system, *C. elegans*. Significantly, Parrish reports that dsRNA triggers having 14 and 23 uninterrupted nucleotide identity to the target induced no interference. P. 1079, right col. Parrish does show that certain chemical modifications are tolerated in long (742 nucleotide long) double stranded RNA constructs (e.g., 2'-aminouridine, 2'-deoxythymidine, 2'-fluorouridine or 5-iodouridine). However, Parrish, which was published before Elbashir, did not provide teachings sufficient to allow

Elbashir to successfully modify short interfering RNAs as are presently claimed. Neither Parrish nor Elbashir teach VEGFr1 as a target for RNA interference using short interfering nucleic acids. Pavco, Matulic-Adamic and Cook teach non-analogous art, specifically ribozymes and antisense. Furthermore, as explained in more detail below, application of the long dsRNA teachings of Parrish, and the ribozyme and antisense art of Pavco, Matulic-Adamic and Cook, to siRNAs, was attempted by Elbashir. However, Elbashir failed in arriving at siRNAs with modifications beyond replacement of the 3'-terminal nucleotides with deoxythymidine, let alone modified nucleic acid molecules targeting VEGFr1 as presently claimed. None of these cited references either individually or in combination make obvious the claimed invention.

The Examiner's position goes no further than suggesting that it would have been obvious to try targeting VEGFr1 with siRNA molecules as taught by Elbashir, and that it would have been obvious to try using chemical modifications taught by non-analogous ribozyme and antisense art. Without acquiescing to the position, even if it were true, such position is not the correct standard for judging non-obviousness of the presently claimed invention, i.e., a method of cleaving RNA comprising SEQ ID NO:2456 encoded by a mammalian VEGFr1 gene comprising contacting a double-stranded nucleic acid molecule with the RNA encoded by VEGFr1 gene under conditions suitable for the cleavage of the RNA encoded by the mammalian VEGFr1 gene, wherein: (a) each strand of the double-stranded nucleic acid molecule comprises about 18 to about 27 nucleotides; (b) each strand of the double stranded nucleic acid molecule comprises *one or more chemical modifications selected from the group consisting of 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoro nucleotide, and 2'-deoxy ribose moiety*; and (c) one of the strands of the double stranded nucleic acid molecule is complementary to RNA encoded by the mammalian VEGFr1 gene or a portion thereof and the other strand is complementary to the first strand (*emphasis added*). Moreover, the subsequent prior art establishes that such suggestions failed in relation to siRNA technology as presently claimed, and this was the status of understanding in the art as of the time of the present invention.

One of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Elbashir (*EMBO J*) is the only reference cited that teaches a structure of the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. Pavco teaches ribozymes that target VEGFr1 gene expression. Although ribozymes are a nucleic acid based technology, they differ substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs described by Elbashir (*EMBO J*).

Elbashir attempted to apply chemical modifications to siRNA based on the teachings of the prior art (*i.e.*, Parrish in teaching limited modification of long dsRNA, Matulic-Adamic in teaching ribozyme modifications, and Cook in teaching antisense modifications) but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of pages 6881 and 6882 of Elbashir describes 2'-deoxy and 2'-O-methyl modified siRNA duplexes and is reproduced below:

To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where 2'-O-methyl substitutions were used, this modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbashir,

2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Based on the teachings of "[t]he siRNA Users Guide" from Elbashir, for example, one of skill in the art would not have been motivated to make any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not have been motivated to pursue the presently claimed invention. This is evident from the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Elbashir and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g., Bitko et al., 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar et al., 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA*; *Holen et al., 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6*). These prior art references demonstrate that Elbashir taught away from the presently claimed invention.

Further, a plain reading of Elbashir teaches that 2'-O-methyl modifications are not tolerated and likely interfere with protein associated of siRNP assembly. As such, Elbashir does not provide any motivation to a person skilled in the art to take the teachings of the prior art (e.g., long dsRNA, antisense or ribozymes) and apply it to double stranded RNA molecules as presently claimed because Elbashir tried this approach and failed; Elbashir therefore teaches away from using modifications beyond the use of 2'-deoxynucleotides at the 3'-terminal positions of the double stranded RNA molecules. One of skill in the art would not have been motivated to incorporate 2'-O-

methyl, 2'-deoxy-2'-fluoro and 2'-deoxy ribose (abasic) modifications into the double stranded RNA molecules as presently claimed.

The applicants have shown that 2'-O-methyl, 2'-deoxy-2'-fluoro and 2'-deoxy ribose (abasic) modifications are well tolerated in double stranded nucleic acid molecules targeting VEGFr1 gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully target VEGFr1 gene expression. For example, in the present application and in co-pending application Nos. USSN 10/758,155, published as US-2005-0075304, USSN 10/831,620, published as US-2005-0148530, USSN 10/844,076, published as US-2005-0171039, USSN 10/944,611, published as US-2005-0233998, and USSN 10/962,898, published as US-2005-0222066, applicant has designed, synthesized, and tested 2'-O-methyl, 2'-deoxy-2'-fluoro and 2'-deoxy ribose (abasic) modified double stranded nucleic acid molecules of the claimed invention with potent activity against VEGFr1 gene expression. The instant application, along with other co-pending applications, demonstrate that application of 2'-O-methyl, 2'-deoxy-2'-fluoro and 2'-deoxy ribose (abasic) modifications to double stranded nucleic acid structures are well tolerated for maintaining potent RNAi activity against VEGFr1 and other target nucleic acid sequences.

For all of the reasons stated above, a person skilled in the art would not have been motivated to follow the teachings of Elbashir, let alone the long dsRNA, antisense or ribozyme art to make and use the chemically modified double stranded nucleic acid molecules of the present invention to target VEGFr1.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success

is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000).

Applicant submits that no prima facie case of obviousness exists because, as described above, there would be no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach against the instant claims. Because no prima facie case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims. Clarification of the claims by virtue of the present amendments further obviates the rejection.

The foregoing argument as to why the combination of cited references do not render the present claims obvious is further substantiated by the enclosed Declaration under 37 C.F.R. 1.132 of inventor James McSwiggen. In his Declaration, Dr. McSwiggen explains why those working in the RNAi field at the time of the present invention would not have been motivated by the teachings of the long double stranded RNA (Parrish), antisense (Cook) and ribozyme (Matulic-Adamic and Pavco) arts to make the modifications recited in the present claims, nor would they have a reasonable expectation of successfully applying those teachings to obtain the presently claimed invention.

As Dr. McSwiggen explains, there are significant structural differences between long double stranded RNA, antisense oligonucleotides and ribozymes on the one hand and siRNAs on the other. Studies had shown that enhancing stability of antisense oligonucleotides and ribozymes was critical to achieving optimal activity. The relatively high potency of siRNAs, however, suggested that no additional stability-inducing

modifications would be necessary. Furthermore, it was common knowledge that single stranded nucleic acids were more susceptible to nuclease attack compared to double stranded nucleic acids such as siRNAs. Dr. McSwiggen also notes that teachings within the RNAi art (specifically Elbashir *et al.* 2002 Methods 26:199-213) explicitly taught a desired protocol for siRNA synthesis in which only the terminal TT was modified (as dTdT). For these reasons, Dr. McSwiggen explains, the antisense art and ribozyme art would not supply those skilled in the art with a suggestion or motivation to modify siRNAs in a manner similar to modifications made to antisense oligonucleotides and ribozymes.

Dr. McSwiggen further explains that the art provided no guidance as to the sorts of modifications of siRNA that would lead to the presently claimed invention. (*See* paragraphs 12 *et seq.*) Dr. McSwiggen describes several critical structural and functional distinctions between antisense oligonucleotides and ribozymes on the one hand and siRNA's on the other and explains why one of ordinary skill in the RNAi field would not apply the teachings from the antisense and ribozyme arts to siRNAs.

Dr. McSwiggen also explains that the most relevant art at the time, that is, art dealing directly with modified siRNAs, provided data and other teachings suggesting that extensive modifications of siRNAs was undesirable, discouraging the present inventors and likely steering others in the field away from exploring chemical modifications of siRNAs beyond replacing the 3'-terminal positions.

Based on the foregoing, Dr. McSwiggen concludes that at the time of the present invention those skilled in the art would not be motivated to apply, in particular, 2'-O-methyl, 2'-fluoro, or 2'-deoxy ribose (abasic) modifications to siRNAs merely because such modifications were used to stabilize antisense and ribozymes. Indeed, Dr. McSwiggen notes, the RNAi literature demonstrated that knowledge derived from antisense and ribozymes regarding stabilization could not be readily applied to siRNAs. And, as Dr. McSwiggen further attests, because the mechanism of action between

antisense and ribozymes on the one hand and siRNAs on the other differed so significantly, those skilled in the art would have believed, as the present inventors discovered, that teachings from the antisense and ribozyme arts could not be directly applied to siRNAs.

For the reasons set forth above, Tolentino et al. (US 2004/0018176), in view of Pavco et al. (US 6,346,398), Elbashir et al. (EMBO J., 20:6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, 1077-1087, 2000), Matulic Adamic et al. (US 5,998,203) and Cook et al. (US 5,587,471) do not teach or suggest a method of cleaving RNA comprising SEQ ID NO:2456 encoded by a mammalian VEGFr1 gene comprising contacting a double-stranded nucleic acid molecule with the RNA encoded by VEGFr1 gene under conditions suitable for the cleavage of the RNA encoded by the mammalian VEGFr1 gene, wherein: (a) each strand of the double-stranded nucleic acid molecule comprises about 18 to about 27 nucleotides; (b) each strand of the double stranded nucleic acid molecule comprises one or more chemical modifications selected from the group consisting of 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoro nucleotide, and 2'-deoxy ribose moiety; and (c) one of the strands of the double stranded nucleic acid molecule is complementary to RNA encoded by the mammalian VEGFr1 gene or a portion thereof and the other strand is complementary to the first strand with a reasonable expectation of success. Because there would be no motivation to combine the cited references and because there would be no reasonable expectation of success in such a combination, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

**CONCLUSION**

Applicant respectfully requests the claim amendments to be entered and the remarks considered. Applicant believes that with this amendment, the claims are in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,  
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